

SCIENTIFIC LETTER



Intermediate- versus prophylactic-dose heparin for hospitalised patients with COVID-19: an updated meta-analysis of randomised trials

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Dear Editor,

At the outset of the COVID-19 pandemic, many randomised trials were established to explore whether the use of anticoagulants, mostly unfractionated heparin and low-molecular-weight heparins, might be effective in combatting the increased risk of thromboembolic events and related deaths [1, 2] in patients with COVID-19 requiring hospitalisation. Findings from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Prospective meta-analysis (PMA) [3] showed no evidence that, compared to prophylactic-dose heparins, intermediate-dose heparins reduced 28-day mortality [Odds ratio (OR) 0.95, 95% CI 0.76–1.19] based on data from 10 randomised trials (3897 patients). However, there was a suggestion that any mortality advantage of intermediate-dose heparins might be limited to critically ill patients—defined as those who required non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV) at randomisation (interaction *p* value 0.10).

More recently, results based on 1255 patients recruited between April 2021 and November 2023 to the REMAP-CAP trial have been reported [4]. REMAP-CAP randomised patients with COVID-19 receiving NIV or IMV to receive either intermediate-dose heparin or standard (prophylactic) dose. For their primary outcome of organ support free days, findings were inconclusive.

The objective of our letter is, therefore, to provide a brief update of the evidence, incorporating relevant results from REMAP-CAP alongside data included in the

WHO REACT PMA. We have completed meta-analyses based on all patients and separately restricted to those receiving NIV or IMV at randomisation, for the three main outcomes of 28-day all-cause mortality (primary outcome), arterial or venous thromboembolic events and major bleeding.

We estimated separate ORs using frequency count data for the pre- and post-response adaptive randomisation periods from REMAP-CAP and pooled these to obtain overall estimates of treatment effect for each of the three outcomes for the trial (see Supplementary Table S1). These ORs were then combined in a frequentist fixed-effects meta-analysis alongside the existing trials following methods that have been previously reported [3].

Descriptions of REMAP-CAP and the 10 trials from the original WHO REACT PMA [3] are given in Supplementary Table S2. The updated meta-analysis includes data from 11 trials (5151 hospitalised patients) and gave OR estimates of 0.96 (95% CI 0.80–1.14) for 28-day mortality; 0.78 (95% CI 0.60–1.02) for thromboembolic events and 1.10 (0.67–1.79) for major bleeding, largely consistent with findings from the original meta-analysis with no clear evidence of a benefit of intermediate- compared to prophylactic-dose heparins (Fig. 1a and Supplementary Figures S1–S3).

Based on data from 2065 patients receiving NIV or IMV at randomisation from 9 trials gives OR estimates of 0.90 (95% CI 0.72–1.11) for 28-day mortality; 0.79 (95% CI 0.58–1.06) for thromboembolic events and 1.04 (95% CI 0.59–1.82) for major bleeding. Again, these results are broadly consistent with the original meta-analysis and indicate that compared with prophylactic dose, there is no strong evidence that intermediate

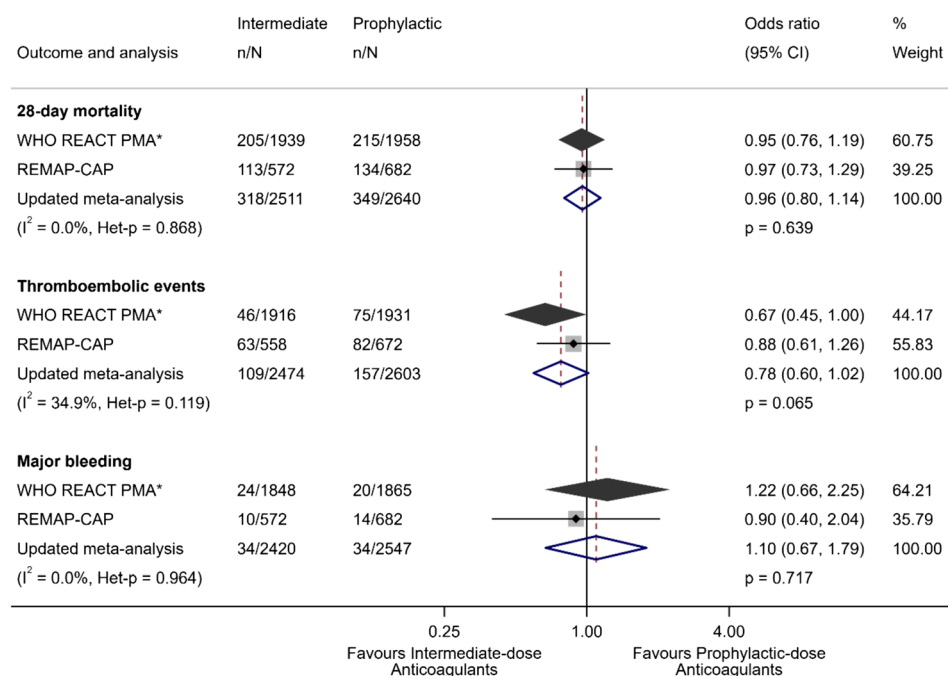
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(a) All hospitalised patients with COVID-19



(b) Patients with COVID-19 receiving non-invasive or invasive mechanical ventilation at time of randomisation

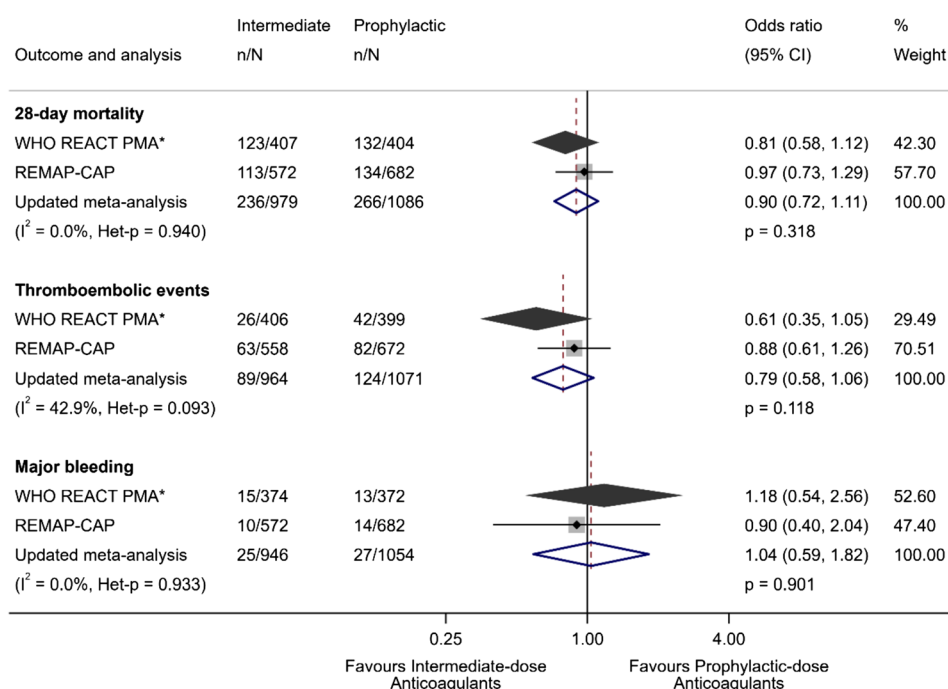


Fig. 1 Association of intermediate- versus prophylactic-dose anticoagulation with 28-day mortality, thromboembolic events and major bleeding for patients with COVID-19. Results are presented from (i) the WHO REACT prospective meta-analysis [3], (ii) the REMAP-CAP trial [4], and (iii) an updated meta-analysis including the REMAP-CAP trial. **a** All hospitalised patients with COVID-19. *WHO REACT PMA refers to WHO Rapid Evidence Appraisal for COVID-19 Therapies Prospective meta-analysis. I^2 95% confidence intervals are [0.0%, 51.2%], [0.0%, 66.9%] and [0.0%, 58.5%] for the three outcomes respectively. **b** Patients with COVID-19 receiving non-invasive or invasive mechanical ventilation at time of randomisation. *WHO REACT PMA refers to WHO Rapid Evidence Appraisal for COVID-19 Therapies Prospective meta-analysis. I^2 95% confidence intervals are [0.0%, 56.3%], [0.0%, 73.2%] and [0.0%, 64.1%] for the three outcomes respectively

dose thromboprophylaxis reduces 28-day mortality or thromboembolic events or increases major bleeding (Fig. 1b and Supplementary Figures S4–S6). Note that to avoid potential aggregation bias, these estimates should not be compared with those obtained for patients not receiving NIV or IMV [5].

Obtaining frequency counts pre- and post-response adaptive randomisation periods enabled us to fully account for the design of REMAP-CAP whilst maintaining the frequentist design of the PMA in this update. Inclusion of REMAP-CAP has added weight to the original findings whilst not substantively changing interpretation. In all hospitalised patients, and in those who required NIV or IMV at randomisation, we find no strong evidence that compared with prophylactic dose, intermediate-dose heparins reduced mortality or thromboembolic events, or increased major bleeding. Neither the original nor this updated meta-analysis assessed the outcome of organ support free days, the primary outcome measure reported in REMAP-CAP. Although the original trials in the PMA recruited patients far earlier in the pandemic compared with REMAP-CAP, there was no meaningful statistical heterogeneity for 28-day mortality in the updated meta-analysis, with most results consistent with the REMAP-CAP trial.

Prompt inclusion of results from REMAP-CAP has been possible by building on the original collaborative and prospectively designed meta-analysis [6], which also provided detailed results from each trial that allowed us to restrict the meta-analysis population to those requiring NIV or IMV. Although this reduced clinical heterogeneity, aiding interpretation, it also considerably reduced the total number of eligible patients, and therefore overall power, despite the substantial contribution from REMAP-CAP. Important to note is that our study defined critically ill based on a requirement for NIV/IMV, and so findings may not be applicable to patients with other critical complications from COVID-19 (e.g. heart failure).

In conclusion, whilst administration of intermediate-dose heparins does not appear to increase the risk of major bleeding, there is no evidence to indicate that it reduces the risk of mortality or thromboembolic events compared to prophylactic-dose heparins for all hospitalised patients with COVID-19 or for those requiring NIV or IMV. Taken alongside the lack of a clear improvement in organ support free days from REMAP-CAP, there is no strong rationale to support intermediate-dose thromboprophylaxis as a treatment option for patients hospitalised with COVID-19.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-025-08128-0>.

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Data availability

All data contained within this manuscript is aggregate level data, which is available from the supplementary figures.

Declarations

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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